Reviewer #1:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Accept (General priority)
Specific Comments to Authors: This manuscript is generally satisfactory, but the literature review as well as the discussion section are too brief and many relevant literature are not covered, and the authors are advised to further revise the literature review and discussion.

Response 1: The literature review and discussion are brief because they focus on studies that are like the present study. We have included recent literature that illustrates the outlined constraints of studies focusing on biomedical and biophysical morbidity.

Turns out, most literature about affective disorder morbidity focuses on comorbid psychiatric disorders or at most one and sometimes two or three biomedical and biophysical disorders. A detailed review of those constrained types of studies distracts from the main point of this paper, being that there is a dearth of whole population studies that focus on the full range of biomedical and biophysical disorders associated with affective disorders. In essence, most morbidity studies are constrained, unlike this study, a first of its kind and represents the advent of big population data analysis. This type of study and other papers based on this dataset have contributed to the formation of the WPA Morbidity Section.

The WPA Section chair (wpanet/comorbidity) has flagged the study of biomedical and biophysical morbidity as one of psychiatry's main 21st century challenges. Further, the main point of the reproducible literature review outlined in Table 1 was to highlight the lack or 'big-data' or epidemiological population-based studies of the subject.

Based on the present results, a paradigm shift is required in terms of how we conceptualize, define, and study morbidity.

We have included reference to these ideas by defining biomedical and biophysical morbidity in the title, abstract, introduction, and we have included discussion and references to the above in the discussion.

Reviewer #2:
Scientific Quality: Grade A (Excellent)
Language Quality: Grade A (Priority publishing)
Conclusion: Minor revision
Specific Comments to Authors: This article is an excellent illustration of the high rates of comorbidity among psychiatric disorders. The novel method of analysis of the population-based sample provides further insight into the complex nature of comorbidity in affective disorder.

I had a few minor issues about the way the results have been presented.

ABSTRACT Introduction & objectives are similar. Ideally, a background of one or two sentences can be provided. Objectives (Aims) of the study should be separated from the background.
Response 2: Adapted in abstract.

The meaning of the terms “biomedical and biophysical morbidity” is not exactly clear. What is the distinction between them?

Response 3: Adapted in abstract.

If the authors mean psychiatric and physical comorbidity, why not use these terms instead? Other terms such as “comprehensive temporal hyper-morbidity” need to be explained.

Response 4: Among the first papers published, the individual who inspired the original study (Vincent Felitti) suggested to me (verbal communication) using biomedical and biophysical morbidity as the main term, when we first used the term ‘physical comorbidity’. In this paper we will stay with the terms as described, as the term “biomedical and biophysical morbidity” has appeared in the papers published up to this point based on this dataset:

1. Cawthorpe D, Chai T. (2023) Cardiovascular disease and mental disorder associated temporal hyper-morbidity in a population: A novel representation of diagnosis frequency. (in press: Neuropsychiatry).
2. Cawthorpe D. (2023). A population-based model for rationing COVID-19 vaccine. Qeios. doi:10.32388/HISNX4.
3. Chai PH, Chang S, Cawthorpe D. (2021) The Temporal Hyper-Morbidity of Asthma and Attention Deficit Disorder: Implications for Interpretation Based on Comparison of Prospective and Cross-Sectional Population Samples. Psychiatry Investig. 2021 Feb;18(2):166-171. doi: 10.30773/pi.2020.0349. Epub 2021 Feb 22. PMID: 33601870; PMCID: PMC7960750.
4. Cawthorpe D. (2021) A comparative epidemiology model for understanding mental morbidity and planning health system response to the COVID-19 pandemic. Heart & Mind. 1:5(4): 103-111. DOI:10.4103/hm.hm_60_2.
5. Cawthorpe D (2018). A 16-Year Cohort Analysis of Autism Spectrum Disorder-Associated Morbidity in a Pediatric Population. Front. Psychiatry, 29 November 2018. doi.org/10.3389/fpsyt.2018.00635.
6. Cawthorpe, D. Kerba, M. Narendran, A. Ghuttora, H. Chartier, G. & Sartorius, N. (2018). Temporal order of cancers and mental disorders in an adult population. BJPsych Open, 4(3)., 95-105. doi:10.1192/bjo.2018.5
7. Cawthorpe, D. (2017). Comprehensive Description of Comorbidity for Autism Spectrum Disorder in a General Population. Perm J 2017; 21:16-088. https://doi.org/10.7812/TPP/16-088 E-pub: 12/23/2016
8. Anwar S. Cawthorpe D. (2016). What “big population data” tells us about neurological disorders comorbidity. JHA, 5(6).: 1-8. (doi 10.5430/jha.v5n6p75).

9. Chartier G. Cawthorpe D. (2016). From 'Big 4' to 'Big 5': a review and epidemiological study on the relationship between psychiatric disorders and World Health Organization preventable diseases. Current Opinions in Psychiatry. September 2016; 29 (5).: 316-321.
10. Chartier G. Cawthorpe D. (2016). Distinction between Episodic Mood Disorder and Attention Deficit Disorder with Hyperactivity based on their Association with the Main Classes of International Classification of Disease in a Child and Adolescent Population. Ann Depress Anxiety. 3(1).: 1073.
11. Cawthorpe D. Davidson M. (2015). Temporal Comorbidity of Mental Disorder and Ulcerative Colitis. Perm J. Winter; 19(1).: 52-57.
12. Cawthorpe D. Chartier G. (2014). Population: Implications for Future Society. Review of Social Studies, Law and Psychology. Vol. 8: 48-54.
13. Ghuttora H. Cawthorpe D. (2013). Treatment of physical disorder in children with mental disorder: A health care utilization study. Journal of Hospital Administration. DOI: 10.5430/jha.v3n2p24 http://www.sciedu.ca/journal/index.php/jha/article/view/3131).
14. Lui J. Narendran A. Cawthorpe D. (2013). What can population-based physician billing data tell us about the prevalence, costs and disorders associated with different types of cancers based on the 16 year prevalence of cancer diagnosis? Journal of Hospital Administration. 2014, Vol. 3, No. 4: 9-19
15. Cawthorpe D. (2013). A Novel Population-Based Health Index for Mental Disorder. Perm J Spring; 17 (2).:50-54. (http://www.thepermanentejournal.org/issues/2013/spring/5101-mental-disorder.html).
16. Wilkes T. Guyn L. Li B. Lu M. Cawthorpe D. (2012). Association of child and adolescent psychiatric and biomedical/somatic disorders: Do population-based utilization study results support the Adverse Childhood Experiences study? The Permanente Journal Spring; 16 (2).: 21-24.
17. Cawthorpe D. Wilkes T. Guyn L. Li B. Lu M. (2011). Association of mental health with health care utilisation and cost: A population study. Canadian Psychiatric Journal 56 (8). 490-494.

Response 5: Further, it was Jakovljevic's (in references) defining paper "Comorbidity and multimorbidity in medicine today: challenges and opportunities for bringing separated branches of medicine closer to each other" that brought us to the concept and term ‘temporal hyper-morbidity’ (over-representation of diseases over time, either before or after the index diagnostic event, in this case affective disorder).

Now adapted into the text of abstract and introduction: “’temporal hyper-morbidity’ (over-representation of diseases over time, either before or after the index diagnostic event)”…

INTRODUCTION The references stated in the first line (Numerous studies have examined the comorbidity of affective disorders and other mental processes and disorders 1–9) are a bit puzzling since there are more comprehensive reviews of medical comorbidity in mood disorders.

For example –
Schaffer et al. Ann Clin Psychiatry. 2012 Feb;24(1):6-22
Response 6: We did not include this study as its focus is on psychiatric-associated psychiatric morbidity, not on biomedical and biophysical morbidity.

Ramasubbu et al. Ann Clin Psychiatry. 2012 Feb;24(1):82-90
Response 7: Included in discussion with reference to the paper being constrained in its conceptualization of morbidity.

Kilbourne. Bipolar Disord. 2004 Oct;6(5):368-73
Response 8: Included in discussion – constrained sample of Veterans.

McIntyre et al. Ann Clin Psychiatry. 2012 May;24(2):163-9
Response 9: Systematic qualitative review – not included as data focus is different from current paper.

Krishnan. Psychosom Med. 2005 Jan-Feb;67(1):1-8
Response 10: Systematic review – not included as data focus is different from current paper.

METHODS One of the authors' stated objectives was to – "…present the current state of the art of biomedical and biophysical morbidity associated with mental disorder in large population-based samples in the published literature (PubMed)." Although the authors have stated that standard methodology was not followed, the details of these PubMed searches are still too sketchy.

Response 11: Now embedded in text:
The details of each listed search result in PubMed recorded in Table 1 are repeatable. The results precisely list the total number of papers in each search. The position of the search (eg, Title or MESH) indicates the importance of the terms in the search. In the results, quotients are expressed in the terms of the results (#publications) for the numerator expressed as a fraction of the results in generic search (unspecified position) for the denominator (#publications). This quotient is an indicator the magnitude of epidemiological papers as a function of all papers and is presented in the text below Table 1 and discussed in the first paragraph of the discussion.

Moreover, none of the conclusions derived from this search (mentioned in the discussion) can be made out from Table 1.

Response 12: We have adjusted the description below Table 1 and included one additional line in Table 1 for clarity: The results of Table 1 are noted in the text below Table 1 and again in the first paragraph of the discussion where they are contextualized.

RESULTS Table 2 is a very interesting comparison between individuals with and without affective disorders. But the title of the table appears somewhat incomplete.

Response 13: We agree with the reviewers comment: we have changed the title of Table 2 into "Demographic and diagnosis frequency of groups with and without affective disorder."

Although the text states that – "As well, there are more females than males with affective disorder and they have in total and on average a higher frequency of biomedical and biophysical diagnoses." – the table does not make this clear.

Response 14: We agree with the reviewers' comment. We changed the wording so that the text of Table 2 now orients the reader to the noted observations.

Moreover, if the group without affective disorder includes individuals with other psychiatric disorders, is it possible to conclude that the rates of physical comorbidities are higher in affective disorders than other psychiatric disorders?

Response 15: We disagree with the reviewers comment: The paragraph in 'Population sample description' states in the introductory sentence: "Note that the group without affective disorder consists of individuals without any other mental disorders."

The figures also need more comprehensive descriptions.

For example, I could not understand how this conclusion was derived – "From the full distribution of age-specific proportional ratios distributions shown for males and females in Figures 3 and 6, it is apparent that females have more laboratory testing and procedures, while males have more V code diagnoses"

Response 16: We thank the reviewer for this comment, as it highlights a problem that readers might face with the interpretation of 3D graphics. We therefore added on page 7 paragraph 1: "Note in the following graphs when the frequency of diagnosis ratios for each dependent group is equal to the value one, it means that the ratio of each group is equal. When greater than the value one, the ratio is greater in the group with affective disorders. When less than the value one, the ratio is greater in the group without affective disorders."
AND
"Overall, the reader might take away the following main points of the graphic representations of comparative unique frequency ratios of diagnosis for all ICD-9 diagnoses by age. 1) Those with affective disorder have greater frequencies of unique ICD-9 diagnoses across age. 2) Males are substantially different than females."
AND
"Note the frequency of peaks at the value 1200 on the diagnosis axis comparing males and females, the frequency of V-Code peaks is greater for males. Similarly, note the frequency of peaks of value 1500 on the diagnosis axis comparing males and females, the frequency of Laboratory Testing peaks is greater for females across all ages."

DISCUSSION As mentioned above, the conclusions derived from the PubMed searches are unclear.

Response 15: Adapted in results and discussion as noted above in Response 12.

Apart from the ones mentioned, there are many other methodological lacunae in the current state of research into comorbidity in psychiatric disorders. This could be briefly mentioned in the conclusion.

Response: We thank the reviewer for this comment. We included the following text on page 13 in the paragraph before the conclusions: ”Finally, the foregoing novel analyses are a pointer to the complexity of any understanding of the temporal hyper-morbidity of affective disorders, save any mental disorder. For example, a next level of complexity in analysis requires the calculation of the conditional order of diagnoses within individuals. Conditional order is not simply the frequency of diagnoses for the dependent groups of individuals in time, (total of diagnoses on date 1, 2, 3…n) independent of the diagnosis that each individual experiences before or after any given diagnosis. The conditional sequence of diagnoses within individuals may reveal more information that is relevant to the etiology and prognosis of disorders arising before and after an index diagnosis of affective disorder.”

(1) Science editor:

The manuscript has been peer-reviewed, and it is ready for the first decision.
Language Quality: Grade B (Minor language polishing)
Scientific Quality: Grade C (Good)

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Psychiatry, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office’s comments and the Criteria for Manuscript Revision by Authors. Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example,

“Figure 1 Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...”. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

Response: Figures in a separate file and in text body for your convenience.

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Response: All figures *de novo*, created by authors.

The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the RCA.

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